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Remarks:

This application was filed on 01 - 04 - 1999 as a
divisional application to the application mentioned
under INID code 62.

(54) **Transesterification products of corn oil and glycerol and their use in pharmaceutical compositions**

(57) Transesterification products of corn oil and glycerol having a total palmitic acid and stearic acid content of mono-, di- and tri-glycerides of less than 10% by weight, and a free glycerol content of less than 10 % by weight. Use of these products in pharmaceutical compositions.

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Table (continued)

Bioavailability of Ciclosporin in Humans			
Mean (\pm SD) values of $AUC_{(0-48\text{ h})}$, C_{\max} and T_{\max} after single oral administration of different dosages of Composition X and Composition 8			
400 mg Comp X	3326 \pm 1115	785 \pm 252	2.1 \pm 0.9
400 mg Comp 8	6944 \pm 1468	1557 \pm 286	1.4 \pm 0.4
600 mg Comp X	4501 \pm 1217	917 \pm 236	2.3 \pm 1.0
600 mg Comp 8	9689 \pm 2282	1812 \pm 400	1.7 \pm 0.6
800 mg Comp X	5209 \pm 1554	1045 \pm 264	2.4 \pm 1.0
800 mg Comp 8	12162 \pm 3059	2143 \pm 576	2.1 \pm 0.8

[0076] Based on the mean ratios of $AUC_{(0-48\text{ h})}$ -values the relative bioavailability of Composition 8 vs Composition X was estimated between 170% and 233%, depending on the dose administered (see following table).

Table

Relative bioavailability of Composition 8 vs. Composition X		
Dose of [mg]	Mean ratio of $AUC_{(0-48\text{ h})}$ Comp 8 vs. Comp X	Conversion Factor: Comp X vs. Comp 8
200	1.70	0.59
400	2.09	0.48
600	2.15	0.47
800	2.33	0.43

[0077] **Conclusion:** The composition according to the present invention (Composition 8) has a significantly higher bioavailability in humans be at least factor 1.7 when compared to the commercial form (Composition X).

[0078] The accompanying Figure III provides a graphical plot of the mean $AUC_{(0-48\text{ h})}$ -values of composition X (open triangles) versus those of Composition 8 (solid Circles). AUC -values (in ng.h/ml) of Ciclosporin vertically and dose horizontally as obtained from Example 4.

[0079] The extent of absorption of Composition 8 (in terms of $AUC_{(0-48\text{ h})}$ -values) seemed to be independent of dose, whereas the extent of absorption of Composition X declined with increasing doses (see Figure III).

Claims

1. A trans-esterification product of corn oil and glycerol comprising predominately of linoleic acid and oleic acid mono-, di- and tri-glycerides, and having a free glycerol content less than 10% by weight, wherein the product has been treated so as to

a) reduce the saturated fatty acid component content of mono-, di- and tri-glycerides; and to
b) enhance the unsaturated fatty acid component content of mono-, di- and tri-glycerides so that the linoleic acid and oleic acid mono-, di- and tri-glyceride content is in total 85% by weight or more of the whole composition, and
the product has a total palmitic acid and stearic acid content of mono-, di- and tri-glycerides of less than 10% by weight.

2. A product as claimed in claim 1 having 30% to 40% by weight of mono-glycerides.

3. A product as claimed in claim 1 or claim 2 having 45% to 55% by weight of di-glycerides.

4. A product as claimed in any preceding claim having from about 7.5 to about 15 % by weight of tri glycerides.

5. A product as claimed in any preceding claim having a free glycerol content of less than 5% by weight.
6. A product as claimed in any preceding claim having a free glycerol content of less than 2% by weight.
- 5 7. A transesterification product of corn oil and glycerol having a saturated fatty acid content of mono-, di-, and tri-glycerides, and having a free glycerol content less than 10% by weight, which product comprises
 - i) from about 25% to about 50% by weight of mono-glycerides, from about 30% to about 60% by weight of di-glycerides, and at least 5% by weight of tri-glycerides; and
 - 10 ii) a linoleic acid, oleic acid and linolenic acid mono-, di- and tri-glyceride content of at least 85% by weight; wherein the total palmitic acid and stearic acid content of mono-, di-, and tri-glycerides is less than 10% by weight.
8. A product as claimed in claim 7 having 30% to 40% by weight of mono-glycerides.
- 15 9. A product as claimed in claim 7 or claim 8 having 45% to 55% by weight of di-glycerides.
10. A product as claimed in any one of claims 7 to 9 having from about 7.5 to about 15% by weight of tri-glycerides.
- 20 11. A product as claimed in any one of claims 7 to 10 having a free glycerol content of less than 5% by weight.
12. A product as claimed in any one of claims 7 to 11 having a free glycerol content of less than 2% by weight.
13. A process for obtaining a refined glycerol-transesterified corn oil according to any preceding claim, comprising heating of corn oil with glycerol at high temperature in the presence of a suitable catalyst under an inert atmosphere with continuous agitation to effect glycerol-transesterification, and refining said product by freezing procedures coupled with separative techniques.
- 25 14. A pharmaceutical composition comprising a product as claimed in any of claims 1 to 6.
- 30 15. Use of a product as claimed in any of claims 1 to 6 in a pharmaceutical composition.
16. A pharmaceutical composition comprising a product as claimed in any of claims 7 to 12.
- 35 17. Use of a product as claimed in any of claims 7 to 12 in a pharmaceutical composition.

Claims for the following Contracting States : GR, ES

- 40 1. A process for preparing a trans-esterification product of corn oil and glycerol which product comprises predominately of linoleic acid and oleic acid mono-, di- and tri-glycerides, and having a free glycerol content less than 10% by weight, wherein the product has been treated so as to
 - a) reduce the saturated fatty acid component content of mono-, di- and tri-glycerides; and to
 - 45 b) enhance the unsaturated fatty acid component content of mono-, di- and tri-glycerides so that the linoleic acid and oleic acid mono-, di- and tri-glyceride content is in total 85% by weight or more of the whole composition, and the product has a total palmitic acid and stearic acid content of mono-, di- and tri-glycerides of less than 10% by weight.
- 50 2. A process as claimed in claim 1 wherein the product contains 30% to 40% by weight of mono-glycerides.
3. A process as claimed in claim 1 or claim 2 wherein the product contains 45% to 55% by weight of di-glycerides.
4. A process as claimed in any preceding claim wherein the product contains from about 7.5 to about 15 % by weight of tri-glycerides.
- 55 5. A product as claimed in any preceding claim having a free glycerol content of less than 5% by weight.

6. A process as claimed in any preceding claim wherein the product contains a free glycerol content of less than 2% by weight.
7. A process for preparing a transesterification product of corn oil and glycerol which product comprises a saturated fatty acid content of mono-, di-, and tri-glycerides, and having a free glycerol content less than 10% by weight, wherein the product comprises
 - i) from about 25% to about 50% by weight of mono-glycerides, from about 30% to about 60% by weight of di-glycerides, and at least 5% by weight of tri-glycerides; and
 - ii) a linoleic acid, oleic acid and linolenic acid mono-, di- and tri-glyceride content of at least 85% by weight; wherein the total palmitic acid and stearic acid content of mono-, di-, and tri-glycerides is less than 10% by weight.
8. A process as claimed in claim 7 wherein the product contains 30% to 40% by weight of mono-glycerides.
9. A process as claimed in claim 7 or claim 8 wherein the product contains 45% to 55% by weight of di-glycerides.
10. A process as claimed in any one of claims 7 to 9 wherein the product contains from about 7.5 to about 15 % by weight of tri-glycerides.
11. A process as claimed in any one of claims 7 to 10 wherein the product contains a free glycerol content of less than 5% by weight.
12. A process as claimed in any one of claims 7 to 11 wherein the product contains a free glycerol content of less than 2% by weight.
13. A process for obtaining a refined glycerol-transesterified corn oil according to any preceding claim, comprising heating of corn oil with glycerol at high temperature in the presence of a suitable catalyst under an inert atmosphere with continuous agitation to effect glycerol-transesterification, and refining said product by freezing procedures coupled with separative techniques.
14. A trans-esterification product of corn oil and glycerol comprising predominately of linoleic acid and oleic acid mono-, di- and tri-glycerides, and having a free glycerol content less than 10% by weight, wherein the product has been treated so as to
 - a) reduce the saturated fatty acid component content of mono-, di- and tri-glycerides; and to
 - b) enhance the unsaturated fatty acid component content of mono-, di- and tri-glycerides so that the linoleic acid and oleic acid mono-, di- and tri-glyceride content is in total 85% by weight or more of the whole composition, whereinthe product has a total palmitic acid and stearic acid content of mono-, di- and tri-glycerides of less than 10% by weight; 30% to 40% by weight of mono-glycerides, 45% to 55% by weight of di-glycerides, from about 7.5 to about 15 % by weight of tri-glycerides, and the free glycerol content is less than 2% by weight.
15. A pharmaceutical composition comprising a product as claimed in claim 14.
16. A transesterification product of corn oil and glycerol having a saturated fatty acid content of mono-, di-, and tri-glycerides, and having a free glycerol content less than 10% by weight, which product comprises
 - i) from 30% to 40% by weight of mono-glycerides, from 45% to 55% by weight of di-glycerides, and about 7.5% to about 15% by weight of tri-glycerides; and
 - ii) a linoleic acid, oleic acid and linolenic acid mono-, di- and tri-glyceride content of at least 85% by weight; wherein the total palmitic acid and stearic acid content of mono-, di-, and tri-glycerides is less than 10% by weight, and the free glycerol content is less than 2% by weight.
17. A pharmaceutical composition comprising a product as claimed in claim 16.

